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TITLE: Evaluation of the Effects of Multiple Immunizations Administered in a Stressful Environment on Immunologic Function

PRINCIPAL INVESTIGATOR: Kevin L. Russell, M.D.
Margaret A. K. Ryan, M.D.

CONTRACTING ORGANIZATION: Naval Health Research Center
San Diego, California 92186-5122

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Kevin L. Russell, M.D. and Margaret A. K. Ryan, M.D.

E-mail: russell@nhrc.navy.mil

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14. ABSTRACT
Background: It is hypothesized that multiple vaccinations administered simultaneously in a stressful environment may induce an exaggerated Th2 immune response and adverse health effects. Epidemiological surveys have preliminarily confirmed adverse health effects but not Th2 immune responses in multiply immunized war veterans.
Objective Hypothesis: We propose a prospective clinical trial in a military recruit population (~ 6 5 0t)o test the hypothesis that multiple, simultaneous vaccinations in a stressful environment induce an exaggerated Th2 immune response in addition to adverse Th2-associated symptoms.
Specific Aims: This study aims to compare the immune responses and health effects in recruits undergoing a multiple, simultaneous vaccination schedule with the s a l e variables in those immunized with a staggered schedule.
Study Design: A Marine recruit population with routine high levels of stress will be split into (I) multiple, simultaneous and (2) staggered vaccination groups. Cytokine and lymphocyte levels in addition to lymphocyte stimulation studies will be performed on blood samples to compare immune responses. Questionnaires, sick call databases, and comprehensive electronic military health databases will be used to compare health outcomes.
Relevance: Immunity to infectious pathogens is critical for maintaining military readiness, but the potential effects of multiple, simultaneous vaccinations are not well known. This study will contribute to existing research on the possible impact of multiple vaccinations administered under stressful conditions.

15. Subject Terms (keywords previously assigned to proposal abstract or terms which apply to this award)
multiple vaccination, immune response, stress, cytokine, Th2, military

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Introduction:

Recruits receive multiple vaccinations as part of their preparation for basic training because the stressful and crowded conditions provide opportunities for outbreaks of disease. In many basic training camps, the majority of vaccinations are given on the same day. In 1997, Rook and Zumla hypothesized that the combination of vaccination schedules, stress of war, and environmental exposures induced an exaggerated humoral immune response and could have resulted in the Gulf War Syndrome. Since previous studies failed to find any immunological differences, lacked a stressful environment, and cytokine levels were not monitored, outcomes are still unknown. We propose a prospective clinical trial with military recruits to test if multiple vaccinations given simultaneously in a stressful environment lead to Th2 cytokine imbalance and associated adverse health effects.

Body:

The purpose of this study is to determine if multiple, simultaneous vaccinations given in a stressful environment induces a Th2 cytokine shift and/or causes adverse health effects.

Participants have been randomly slit into two groups. The first group received the Current Schedule (CS) of vaccinations at the recruit training command (largely simultaneous), and the second group received their vaccinations by a Staggered Schedule (SS), receiving the same shots but split into three different periods throughout boot camp. Table 1 demonstrated the two schedules. Changes to immunologic levels through the three blood draws are being evaluated through the use of lymphocyte stimulation studies. The ratio of Th2 to Th1-associated cytokines will be calculated for the two arms. Saliva and serum levels are also being monitored for cortisol levels, as surrogates for stress levels. Also, visits to the clinic and hospital by all participants have been monitored, and categorizing into specific groups, i.e. respiratory, muscular, GI, and psychological illnesses. Specific tasks outlined in the Statement of Work with status of completion at the time of this reporting follow:

Task 1. Determine if multiple vaccinations administered simultaneously in a stressful environment induce a Th2 immune response or other irregularities in immune function.

a. Perform initial blood draw and analysis to determine baseline immunologic data (day 1).*

Status: Initial blood draw completed on all subjects enrolled.

b. Create two study populations by vaccinating half the total population according to a multiple, simultaneous (MS) vaccination schedule (day 1) and the other half according to a staggered schedule (SS) (days 1 and 35). Three hundred twenty-five individuals will be recruited for each arm of the study. Given attrition (study attrition and recruit camp attrition) of 20%, a total of approximately 260 will remain in each arm, meeting sample size calculation needs.

Status: Enrollment is complete at the present time with 324 CS participants and 331 SS participants enrolled. Attrition is currently at 17.8%. As of 19 April 2006, all remaining participants will have completed the follow-up portion of the study. The last phase of continued monitoring of visits to clinics and hospitals will last approximately for one year, per the protocol.

c. Perform blood draws for immunologic analyses detection of immune response (days 1, 30 and 45).

Status: Performed on all remaining participants (attrition is the result of, among other reasons, removal from training, and return to home). The final (day 45) visit and blood draw remains for only the final 2 enrolled divisions (n=79)

d. Compare cytokine profile and immune function indicator data between MS and SS groups (completed by first year of study).

Status: Lab work is in-progress. Pending results

Task 2. Determine if the multiple vaccinations administered simultaneously in a stressful environment lead to adverse health effects that are proportional to the Th2 shifts.

a. Administer initial questionnaire to determine baseline symptomologic health data (day 1).

Status: Completed.

b. Create two study populations, MS and SS, as indicated above (days 1 and 35).

Status: Completed.

c. Perform passive surveillance of subject health through sick call databases for the duration of training to assess short-term effects (days 1-84).

Status: Completed.

d. Administer final questionnaire to determine symptomologic health changes throughout training (day 70).

Status: Ongoing.

e. Perform passive surveillance of subject health through comprehensive medical databases for one year after the completion of training to assess long-term effects (completed by second year of study).

Status: Ongoing.

f. Compare health-effect data between MS and SS groups (completed by second year of study).

Status: Ongoing.

Table 1

Vaccination Schedules	Day 1	Day 30	Day 45
Current Vaccination Schedule (CS)	Meningococcal MMR (live) Hepatitis A/B #1 Tetanus-diphtheria IPV Varicella #1 (live) Yellow fever (live)	Hepatitis A/B Varicella #2 (live)	
Staggered Vaccination Schedule (SS)	Meningococcal MMR (live) Varicella #1 (live)	Varicella #2 (live) Yellow Fever (live)	IPV Hepatitis A/B #1 Tetanus-diphtheria
Phlebotomy and Questionnaire Schedule (all subjects)*	Phlebotomy Questionnaire Saliva Sample	Phlebotomy Saliva Sample	Phlebotomy Questionnaire Saliva Sample

Key Research Accomplishments:

1. The project was presented at the Navy Occupational Health and Preventive Medicine Workshop, Virginia Beach, VA, 19-23 Mar 2006. The poster won a first place ribbon. Abstract is attached in the Appendix

Reportable Outcomes:

Clinic visits to date by participants in the two arms have yielded slightly different outcomes. Among participants receiving the Current Schedule, the rate of visits to the medical clinic for all causes was 22.8/100 person-weeks. In the Staggered Schedule, the rate was 20.6/100 person-weeks. This difference was largely found in clinic visits for respiratory complaints. Final analysis of health care utilization will include data up to one year out, per the protocol.

Conclusions:

The final follow-up is pending for the last 2 enrolled Divisions, and laboratory processing is in-progress. Data analysis has not been performed; thus, no conclusions can be made at the present time.

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Abstract presented to the Navy Occupational Health and Preventive Medicine Workshop, Virginia Beach, VA, 19-23 Mar 2006.

EVALUATION OF THE EFFECTS OF MULTIPLE VACCINATIONS ADMINISTERED IN A STRESSFUL ENVIRONMENT ON IMMUNOLOGIC FUNCTION.

CDR KEVIN RUSSELL, MC, USN; CHRIS MYERS, PHD; LCDR PAUL A ANDRE, MSC, USN; JENNIFER STRICKLER; CDR MARGARET RYAN, MC, USN; AND THE GREAT LAKES TRAINING COMMAND RESEARCH TEAM. NAVAL HEALTH RESEARCH CENTER, P.O BOX 85122, SAN DIEGO, CA 92186-5122; BRANCH HEALTH CLINIC MEDICAL IN-PROCESSING, NAVAL HOSPITAL GREAT LAKES, 1020 11TH AVE; BLDG 1523, GREAT LAKES, IL 60088

Background: Since the end of the Persian Gulf War, there have been reports of unexplained, multi-symptom illnesses afflicting veterans who served in that conflict. Several factors were cited as potentially prompting this effect, including a large antigen load introduced by the simultaneous administration of multiple immunizations in persons experiencing stress. Other reports of poor outcome following multiple simultaneous vaccinations have raised concern over this practice.

Objective: Evaluate the effects of multiple simultaneous vaccinations as compared to a staggered regimen.

Methods: Willing participants at the Great Lakes Naval Training Command are divided into two arms: the first receiving all vaccines largely simultaneously per the command routine, and the second receiving the same vaccines in a staggered schedule over the 8 weeks of training. Blood draws for lymphocyte stimulation studies, baseline/end-of-training symptom and performance questionnaires, and sick call visit monitoring augment the study. Using electronic data sources, in-patient and out-patient visits will be followed for 1 year following graduation from recruit training.

Results: To date, nearly 400 recruits have been enrolled in this study. Study enrollment and analysis of all samples and data is ongoing (target enrollment 650).

Conclusion: It is unlikely that any one exposure or experience among our Gulf War Veterans will ever explain the adverse outcomes they have experienced. However, as we are able, testing potential hypotheses is critical for understanding and avoiding such exposures in the future.

Recommendation: Identification of safe vaccination practices among our active duty populations should remain a priority.

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